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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,857	11/07/2000	Kathryn Armour	620-117	5675

23117 7590 05/28/2008

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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	PAPER NUMBER
1644	
MAIL DATE	DELIVERY MODE
05/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/674,857	ARMOUR ET AL.	
	Examiner	Art Unit	
	PHUONG HUYNH	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-21, 23-29, 31-33, 37-42, 46-65 and 68-78* is/are pending in the application.

4a) Of the above claim(s) *31* is/are withdrawn from consideration.

5)☒ Claim(s) *71-78* is/are allowed.

6)☒ Claim(s) *16-21,23-29,32,37-41,46-65 and 68-70* is/are rejected.

7)☒ Claim(s) *33 and 42* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 November 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 16-21, 23-29, 31-33, 37-42, 46-65 and 68-78 are pending.

2. Claim 31 stands withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to a non-elected invention.

3. Claims 16-21, 23-29, 32-33, 37-42, 46-65 and 68-70 and newly added claims 71-78 are being acted upon in this Office Action.

4. In view of the claims amendment filed February 25, 2008, the following rejection remains.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

6. Claims 16-21, 23-29, 32, 37-41, 46-65, and 68-70 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "wherein said chimeric CH2 domain is at least **98%** identical to a CH2 sequence (residues 231-340) from human IgG1 or IgG4 having said modified amino acids" in claim 21 (beginning at page 4 of the amendment to the claims) is indefinite because after substituting the blocks of amino acid at 233P, 234V, 235A, 236G, 327G, 330S and 331S in human IgG1 CH2 domain, the sequence identity is at least **95%** (6 substitutions in the full CH2 sequence, which is 110 amino acids in length) rather than the recited 98%. Likewise, substituting the blocks of amino acid at 233P, 234V, 235A, 236G, 327G, 330S and 331S in human IgG2 or IgG4 CH2 domain, the sequence identity is at least 98% (3 substitutions in the full CH2 sequence, which is 110 amino acids in length). One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention. The same reasoning applies to claims 32, 41, 55 and 66. The remaining claims are rejected for depending from said indefinite claims 21, 32, 41, and 55.

Applicants' arguments filed February 25, 2008 have been fully considered but are not found persuasive.

Applicants' position is that since the claims only cover sequences that have the required blocks of amino acids, i.e., 233P, 234V, 235A, 236G and 327G, 330S and 331S, the 98% identity language, in effect, allows a further 2 changes within the (defined, modified) 110 amino acid Ca2 sequence. This represents a reasonable balance between Applicants' contributions and the scope of protection sought.

Applicants agree with the Examiner's analysis of the number of substitutions required to arrive at the "PVAG...GSS" from IgG1 (6 substitutions) and IgG2 and IgGg4 (3 substitutions). However, Applicants do not believe that this creates a contradiction in the claims. The claims explicitly recite: "and wherein said chimeric CH2 domain is at least 98% identical to a CH2 sequence (residues 231-340) from human IgG1, IgG2 or IgG4 *having said modified amino acids"*

By contrast the Examiner appears to reading the claim as follows: "and wherein said chimeric CH2 domain is at least 98% identical to a CH2 sequence (residues 231-340) from human IgG1, IgG2 or IgG4."

That is, the Examiner appears to be overlooking the language "having said modified amino acids". The Examiner is respectfully urged to give careful consideration to this point. It is believed that, having done so, the Examiner will find that the claims satisfy the requirement of 35 USC 112, second paragraph.

In response, if the sequence required the following substitutions at the stated positions 233P, 234V, 235A, 236G and 327G, 330S and 331S in CH2 domain of IgG1 as required by the claim, then the resulting sequence cannot have **98%** sequence identity to the human IgG1. Substituting 6 amino acids from IgG1 "PVAG…GSS" from IgG1 (residues 231-340) in a sequence of 110 amino acids in length ((110-6)/100 is about **95**% sequence identity) to a CH2 sequence of (residues 231-340) form human IgG1. Seven amino acid substitution "E223P, L234V, L235A, no residue at 236...A327G, A330S, P331S" from IgG1 is about 94% identity (claim 32). Three amino acids substitution from IgG2 and IgG4 in a sequence of 110 amino acids is 97% sequence to a CH2 sequence of (residues 231-340) form human IgG1. None of the substitutions mentioned above having said modified amino acids at the stated positions: 223P, 234V, 235A, 236G, 327G, 320S, and 331S amount to **at least 98%** identical to a CH2 sequence residues 231-340 from human IgG1, IgG2 or IgG4 as claimed. Therefore, the claims are indefinite for reasons of record.

7. New grounds of rejections are set forth below.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 16-21, 23-29, 32, 37-39, 41, 46-49 and 50-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 94/29351 publication (published December 22, 1994; PTO 892) in view of Greenwood et al, Eur J Immunol 23: 1098, 1993; PTO 1449).

The WO 94/29351 publication teaches a recombinant binding molecule such as antibody comprising a binding site of antibody such as CDRs capable of binding to a target molecule such as MHC, T-cell receptor, CD4, CD8, CD3, CD28, CD69, CD25 and an effector domain such as human IgG1 Fc having the whole region amino acid residues 233 to 236 (CH2 domain) as numbered with respect to the EU numbering of Kabat is exchanged with the sequence found in human IgG2, and the reference modified antibody has reduced FcRI binding and complement fixation and reduced FcRIII mediated function of IgG1, (see entire document, page 6, lines 1-1220, page 9, lines 4-6, page 9, line 35-36 through page 10, lines 1-22, page 14, line 31-35, Figures 6-12, page 40, claims 17-18, in particular). The reference human IgG1 CH2 domain from residues 233 to 236 intrinsically has the residues E233, L234, L235 and G236 while human IgG2 CH2 domain residues 223 to 2236 intrinsically has the residues P223, V234, A235 and no residue at position 236. The exchanged of residues 233-236 from human IgG1 isotype with human IgG2 at those positions would resulted in E223**P**, L235**V**, L235**A**, and **no residues at 236**. The WO

94/29351 publication teaches the C-terminal half of the CH2 domain affect complement C1q binding and exchanging the G1/G2 lower hinge exchange abolished complement fixation (see page 41, lines 6-36, in particular). The publication further suggests that changing IgG1 residues Pro at **331 to Ser** in the C-terminal half of the CH2 domain is unable to activate complement, see paragraph bridging pages 41-42, in particular. The publication also teaches a process of producing the reference antibody by modifying the nucleotide encoding the reference altered antibody, introducing modified nucleic acid into a host cell comprising the expression vector having the modified nucleotide sequence, culturing the transfected host cell to produce the desire antibody and purify the antibody from the culture (see page 13, lines 24 through page 15, lines 25, page 27, line 10-11, in particular). By choosing appropriate amino acids to alter, it is possible to produce an antibody the ability to which to fix complement is substantially reduced as compared with unaltered parent antibody, see page 8, line 26-31, in particular. The altered antibody with reduced complement fixation and reducing binding affinity to FcγRI and FcRIII is useful for treating various diseases without undesirable toxicity due to complement fixation (see page 11, line 7 through page 12, line 35, pages 40-41, in particular). The application also teaches a preparation comprising the reference antibody and a pharmaceutical acceptable carrier, see claims 8-9 of WO 94/29351 publication, in particular. The WO 94/29351 publication teaches a method of diagnosing or treating disease such as graft vs. host disease, autoimmune arthritis in which the reference antibody molecule is allowed to contact with the desired target molecule such as MHC class I or CD3 under condition to allow binding, see claims 10 and 19 of the publication, page 12, line 21-31, in particular.

The WO 94/29351 publication does not teach the altered antibody having the following residues 327G and 330S in the C-terminus of CH2 from human IgG1 numbered with respect to the EU numbering system.

However, Greenwood et al teach humanized IgG antibody that binds to CAMPATH-1 (also known as CD52) that has the following 327G, 330S and 331S in the CH2 domain. Greenwood et al teach there are only four residues in the C-terminal half of the CH2 domain which differ between human IgG1 and IgG4, see page 1100, col. 2, in particular. These residues are 296 (Tyr vs. Phe), 327 (Ala vs. Gly), 330 (Ala vs. Ser) and 331 (pro vs. Ser), see page 1102, col. 2, second paragraph, Figure 5, in particular). However, changing residues Tyr 296 to Phe, the antibody remained as potent as wild-type for complement lysis, indicating that the failure of IgG4 to activate complement is not due to the lack of Tyr in this position, see page 1101, col. 1,

in particular. With respect to the remaining three residues 327, A330 and P331, substituting the carboxyl-terminal half of the IgG1 CH2 domain with that of IgG4 that contains 327G, 330S, and 331S reduced the killing activity of IgG1 to the IgG4 level (see entire document, page 1101, col. 2, Figure 1, DS111/41, Figure 5, in particular). Greenwood et al teach residues which were essential for mediating antibody dependent cellular cytotoxicity (ADCC) were located in the second half of the CH2 domain, see page 1101, col. 2, in particular). Greenwood et al teach antibody Fc regions are responsible for recruiting host effector mechanisms through activation of complement system, or cellular mediated destruction of target cells through binding to the Fc receptors (FcγRI, FcγRII, or FcγRIII), see page 1098, col.1, in particular. Greenwood et al teach a method of making the reference antibody recombinantly using vector containing nucleotide encoding the reference mutant antibodies, and host cells, see page 1099, Materials and methods, in particular. Greenwood et al teach the critical residues identified pave the way for future modifications to the natural antibody structure, designed to improve their ability to harness natural effector functions, see page 1104, last paragraph, in particular.

Given that WO 94/29351 publication has identified positions E223P, L235V, L235A, and no residues at 236 in the N-terminus of CH2 domain of human IgG1 reduced complement lysis and FcγRI while Greenwood et al has identified the positions A327G, A330S and P331S in the C-terminus of CH2 domain of human IgG1 is unable to activate complement, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the WO 94/29351 publication with the teachings of Greenwood et al to arrive at the claimed invention wherein the binding molecule is capable of binding to any target molecule and wherein the effector domain comprises a chimeric CH2 domain derived from human IgG2 and IgG4 which has the following blocks of amino acids 223P, 234V, 235A, no residue at 236, 327G, 330S and 331S numbered with respect to the EU numbering system of Kabat. Although the prior art does not disclose the altered antibody effector domain is capable of binding to FcγRIIb, the prior art antibodies would have had the inherent property of binding to FcγRIIb to the extent claimed because of the same structure which has the following blocks of amino acids 223P, 234V, 235A, no residue at 236, 327G, 330S and 331S. One of skill in the art would choose from this finite number of identified residues with a reasonable expectation of success absent of any objective evidence of unexpected results. One having ordinary skill in the art would have been motivated to optimize Fc variants of antibody because the WO 94/29351 publication teaches altered antibody with reduced complement fixation and reducing binding affinity to FcγRI and

FcRIII is useful for treating various diseases without undesirable toxicity due to complement fixation (see page 11, line 7 through page 12, line 35, pages 40-41, in particular). One having ordinary skill in the art would have been motivated to optimize Fc variants of antibody because Greenwood et al teach the critical residues identified pave the way for future modifications to the natural antibody structure, designed to improve their ability to harness natural effector functions, see page 1104, last paragraph, in particular.

Given the examination guidelines for determining obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in *KSR International Co. V. Teleflex Inc. 82 USPQ2d 1385 (2007)* and the Examination Guidelines set forth in the Federal Register (Vol. 72, No. 195, October 10, 2007) and incorporated recently into the MPEP (Revision 6, September 2007), the following rationales to support rejection under 35 U.S.C. 103(a) are noted:

A) Combining prior art elements according known methods to yield predictable results.

B) Simple substitution of one known element for another to obtain predictable results.

C) Use of known technique to improve similar products in the same way.

D) Applying known technique to a known product ready for improvement to yield predictable results.

E) "Obvious to try" --- choosing form a finite number of identified, predictable solutions, with a reasonable expectation of success.

F) Some teachings, suggestion, or motivation in the prior art that would lead to one of ordinary skill to modify the prior art reference to arrive at the claimed invention.

Since decreasing ADCC, complement activation and reduced FcγRI and FcRIII binding of an antibody thereby reducing complement mediated cytotoxicity (decreasing side effect) with amino acid substitutions at the 223P, 235V, 235A, and no residues at 236 and 327G, 330S and 331S is desirable and have been predictable at the time the invention was made, there would have been reasonable expectation of success in combine the references teachings to arrive at the claimed invention.

An obviousness is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR International Co. V. Teleflex Inc. 82 USPQ2d 1385 (2007).* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Given that the prior art goal was to make and use therapeutic antibodies with reduced side effects, incorporating amino acid variants at position 223P, 234V, 235A, no residue at 236, 327G, 330S and 331S to decrease side effect due to complement binding for therapeutic antibodies of interest would have been routine to the ordinary skill in the art at the time the invention was made. Claims 21 and 32 are included in this rejection because chimeric CH2 domain having a glycine at position 236 instead of no residue is an obvious variation of teachings of the Greenwood et al who stated that IgG1 at position 236 has a glycine (G) residue, and the glycine residue at position 236 is conserved among IgG1, IgG2 IgG3 and IgG4, see page 1103, Figure 5, in particular. Claims 16-17 are included in this rejection because both references teach nucleic acid encoding the reference antibodies, vector and host and it is within the purview of one of ordinary skill in the art at the time the invention was made to apply conventional methodologies to produce the claimed nucleic acid from the protein. Claims 24-26 and 58-60 are included in this rejection because substituting residues 327G, 330S and 331S from IgG4 into IgG1 within the CH2 domain of the effector retains the effector function of IgG4, i.e. binds to FcγRIIb receptors since only Fc of the IgG4 binds FcγRIIb receptors. The binding of such antibody to FcRIIb expressed on B cells when administering to a patient as taught by the WO 94/29351 publication obviously inhibit B cell activation in vivo and compete with the binding of the second antibody such as autoantibody to the target molecule such as MHC or TCR, CD3 or CD52 as taught by Greenwood et al.

11. Claims 68-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 94/29351 publication (published December 22, 1994; PTO 892) in view of Greenwood et al, Eur J Immunol 23: 1098, 1993; PTO 1449) as applied to claims 16-21, 23-29, 32, 37-39, 41, 46-49 and 50-65 and further in view of Griffin et al (Blood 86: 4430, Dec 1995; PTO 892).

The combined teachings of the WO 94/29351 publication and Greenwood et al have been discussed supra.

The invention in claims 68-70 differ from the combined teachings of the references only in that the binding molecule wherein the target molecule is a human platelet antigen (HPA)-1A.

Griffin et al teach human platelet antigen HPA-1 is the most important platelet alloantigen clinically (see page 4430, col. 1, in particular). Griffin et al teach 98% of the Caucasian population carry HPA-1a (GPIIIa Leu 33), HPA-b1 (GPIIIa pro33) homozygotes are at risk of producing GPIIIa leu 33-specific antibodies after transfusion (post transfusion purpura) or

during pregnancy, against paternally inherited GPIIIa leu 33 present on fetal platelets (neonatal alloimmune thrombocytopenia), see page 4430, col. 1, in particular. Griffin et al teach antibodies that bind to such HPA-1a antigen (see Table 2, in particular) and such antibodies have both diagnostic and potential therapeutic applications, see abstract, page 4435, col. 1, last paragraph, in particular.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the binding domain capable of binding to MHC or T cell receptor or CAMPATH-1 in the antibody as taught by the WO 94/29351 publication and Greenwood et al for the binding domain of the antibody that binds specifically to the target antigen HPA-1 as taught by Griffin et al.

One having ordinary skill in the art would have been motivated to substitute because Griffin et al teach such antibodies that bind to such HPA-1a antigen have both diagnostic and potential therapeutic applications, see abstract, page 4435, col. 1, last paragraph, in particular.

12. Claims 33 and 42 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

13. Claims 71-78 are allowed.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B O'Hara can be reached on (571) 272-0878. The IFW official Fax number is (571) 273-8300.

16. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Primary Examiner, Art Unit 1644
May 23, 2008